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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,433	02/02/2006	Lorenzo Frigerio	1009-0118PUS1	8447
2292 7590 01/25/2008 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747			EXAMINER BRISTOL, LYNN ANNE	
			ART UNIT	PAPER NUMBER
			1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No. 10/535,433	Applicant(s) FRIGERIO ET AL.	
	Examiner Lynn Bristol	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 October 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 34-86 is/are pending in the application.
- 4a) Of the above claim(s) 45, 47, 49, 51, 53-81 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 34-44, 46, 48, 50, 52 and 82-87 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>8/1/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1 and 34-87 are all the pending claims for this application.
2. Claims 1, 34, 35, 38-40, 42-45, 52, 82 and 86 have been amended and new claim 87 was added in the Response of 10/31/07.
3. Claims 45, 47, 49, 51 and 53-81 are withdrawn from examination.
4. Claims 1, 34-44, 46, 48, 50, 52 and 82-87 are all the pending claims under examination.
5. Applicants amendments to the claims have necessitated new grounds for rejection. This action is FINAL.

Information Disclosure Statement

6. The non-patent literature references cited in the IDS of 8/1/07 have been considered and entered.

Withdrawal of Objections

Specification

7. The objection to the specification for failing to provide sequence identifiers for the following sequences, for example, $X_1X_2X_3VSX_4$ on p. 11, lines 11 and 24 is withdrawn in view of the amendment to the specification to include the SEQ ID NO.
8. The objection to the specification for omitting to include the reference citation for "the Frigerio paper" described on p. 3, ¶¶ 1-4 is withdrawn in view of Applicants allegation that the Frigerio references (#3, 11, 12 and 15) cited at the end of the

specification are to be incorporated overcomes the objection. Notably, copies of the Frigerio references (#3, 11, 12 and 15) are provided with the IDS of 5/18/05.

9. The objection to the underlined text occurring at p. 11, line 33 is overcome in view of Applicants amendment to the explain the underlined text. The objection for the underlined text on p. 12, lines 1, 2 and 4; p. 15, line 18; p. 24, lines 29-31; and p. 25, line 5 is also withdrawn.

Claim Objections

10. The objection to Claim 35 for failing to include the article "the" before "nucleotide sequence" is withdrawn in view of the amendment of the claim.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

11. The rejection of Claims 1, 34-44, 46, 48, 50, 52 and 82-86 in lacking antecedent basis for the limitation "the completed heavy chain" in element (b) of Claim 1 is withdrawn in view of the amendment of Claim 1 to recite "the immunoglobulin heavy chain."

12. The rejection of Claims 1, 34-44, 46, 48, 50, 52 and 82-86 for the entire recitation in element (b) of Claim 1 in being unclear as to whether the modification of the nucleotide sequence causes the vacuolar targeting sequence to form a modified nucleotide sequence, or whether the modification occurs in the region of a vacuolar targeting sequence in order to effect its function to target the protein to a vacuole, is withdrawn. The amendment of Claim 1 to recite that the modifying occurs in the region of the C-terminal 18 amino acids to remove or reduce the vacuolar targeting signal obviates the rejection.

13. The rejection of Claims 1, 34-44, 46, 48, 50, 52 and 82-86 in lacking antecedent basis for the limitation "the modified antibody heavy chain" in element (d) of Claim 1 is withdrawn in view of the amendment to recite "a modified immunoglobulin heavy chain."

14. The rejection of Claim 35 for the entire "wherein" clause is withdrawn in view of the amendment of the clause to recite a Markush group for the species of modified nucleotide sequence.

15. The rejection of Claim 35 for the recitation "and/or" is withdrawn in view of the amendment of the claim to recite "and" in view of the introduction of Markush group language.

16. The rejection of Claims 38 and 39 in lacking antecedent basis for the limitation "the heavy chain" is withdrawn in view of the amendment of the claim to recite "an immunoglobulin heavy chain."

17. The rejection of Claim 39 for reciting improper Markush group language is withdrawn in view of the amended claim.

18. The rejection of Claims 40 and 42 in lacking antecedent basis for the limitation "the nucleotide sequence modified" is withdrawn in view of the amendment of the claim to recite "the nucleotide sequence of part (a)."

19. The rejection of Claim 43 in lacking antecedent basis for the limitations: "the modified amino acid" and "the completed heavy chain" is withdrawn. The claim has been amended to recite that "the modified nucleotide sequence encodes a modified amino acid" and "the immunoglobulin heavy chain."

20. The rejection of Claim 43 for the recitation "the modified amino acid is one or both of an isoleucine 3 amino acids and/or 10 amino acids from the C-terminus end of

the completed heavy chain" is withdrawn in view of the amendment of the claim to recite Markush group language for the species of isoleucine positions. However, in amending the claim, Applicants have raised new grounds for rejection discussed below.

21. The rejection of Claim 44 for reciting both broad and narrow range limitations within the same claim is withdrawn in view of the amended claim.

22. The rejection of Claims 52 and 86 in lacking antecedent basis for the limitation "the antibody" is withdrawn in view of the amendment to recite "the antibody molecule."

23. The rejection of Claims 52 and 86 for the recitation "the antibody is subjected to protease digest to for Fab or F(ab')₂ fragments" is withdrawn in view of the amendment to recite "subjected to a protease digest to produce Fab or F(ab')₂ fragments."

Objections Maintained

Specification

24. The objection to the specification for failing to provide sequence identifiers for the amino acid sequences on p. 8, lines 7 and 31 and p. 10, line 31 is maintained.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

25. The rejection of Claim 34 in lacking antecedent basis is maintained. Despite the amendment of Claim 34 to recite "the immunoglobulin heavy chain molecule", the claim still lacks antecedent basis.

26. The rejection of Claim 44 in lacking antecedent basis is maintained. Despite the amendment of the claim to recite "method nucleotide sequence", the claim still lacks antecedent basis.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

27. The rejection of Claims 1, 34-38, 40-44, 46, 48, 50, 52 and 82-86 (and new claim 87) under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

Applicants' allegations on pp. 15-16 of the Response of 10/31/07 and the Declaration of Dr. Vitale have been considered but are not found persuasive.

In the Response, Applicants allege that a written description rejection should be rare; that the modification is only to be performed on the C-terminal 18 amino acids of the immunoglobulin heavy chain and all of the details for performing the modifications are taught in the specification on pp. 5, 6 and 8-12.

The examiner respectfully submits that any modification can be introduced into the 18 amino acid C-terminus of the heavy chain comprising a $\alpha 3$ or mu domain as the claims are interpreted. This could include, *for example*, any one or all of the modifications to any given nucleotide sequence recited in Claim 35:

- a) one or more point mutations
- b) one or more nucleic acid deletions
- c) one or more nucleic acid additions, *and*
- d) one or more nucleotides replaced with a synthetic nucleotide sequence. If a given sequence were to include a modification for each of a-d, then Applicants have not demonstrated a single example of a species falling within the scope much less that the sequence would be reduced in vacuolar targeting signal ability and retain antigen binding activity.

Further, Claim 36 describes another example of a sequence where Xaa2 can be "*any amino acid*" irrespective of its charge, solubility, etc, (and 23 different amino acids exist for each possible substitution) and Applicants have not demonstrated a reasonable number of working embodiments in which "*any amino acid*" could be substituted in the Xaa2 position. A similar comparison can be made to Claims 44 (i.e., X9= *any amino acid*), 45 (Xaa2= independently *any amino acid*), 82 (Xaa2= independently *any amino acid*), and 87 (which depends from Claim 44). Applicants have not demonstrated a reasonable number of species falling within the scope of these claims much less that the sequence would be reduced in vacuolar targeting signal ability and retain antigen binding activity.

The examiner's position is that the specification does not describe a reasonable number of embodiments falling within the scope of generic claim 1 or any one of Claims 35, 36, 44, 45 or 87, and which encodes a heavy chain comprising modified C-terminal 18 amino acids with a reduced or eliminated vacuolar targeting signaling and which still binds an antigen, to support the genus as claimed.

The Declaration of Dr. Vitale is not persuasive on several grounds.

First, Dr. Vitale effectively disavows any priority claim for subject matter of the instant application to the PCT filing date (11/17/2003) and the foreign priority date (11/18/2002). Dr. Vitale asserts that the filing date for the instant application is 5/18/05. It is noted that inasmuch as the instant application entered national stage on 5/18/05, Applicants did not perfect their 102(e) date until 2/2/06 when they filed the executed oath/declaration.

Secondly, Dr. Vitale avers that because only 18 amino acids of the C-terminal end of an immunoglobulin are required to be modified, "there is not an infinite number of possible mutations" and "a sufficient number of representative species of sequences" is demonstrated in the specification.

As discussed in the previous office action and above, Applicants have shown an antibody comprising a modified heavy chain comprising synthetic C-terminal regions for the $\alpha 3$ domain comprising SEQ ID NOS: 7, 8, 9 or 69 and comprising a light chain, where the vacuolarization of the heavy chain is reduced or removed when the protein is expressed in transgenic plant cells, and the antibody molecule has specific binding ability for a given antigen in having both a heavy and light chain. Applicants have not

shown a reasonable number of antibodies could be produced by the method as falling within the full scope of modifications to the C-terminus encompassed by the instant claims and which would also a) have reduced or removed vacuolarization when expressed in any kind of cell and b) retain antigen binding. For these reasons, the rejection is maintained.

Scope of Enablement

28. The rejection of Claims 1, 34-38, 40-44, 46, 48, 50, 52 and 82-86 under 35 U.S.C. 112, first paragraph, in lacking enablement for expressing a functional antibody having only a heavy chain much less any heavy chain with a modified $\alpha 3$ or mu domain, or any transgenic plant- or plant cell-expressed antibody having reduced or removed vacuolar targeting by introduction of just any synthetic nucleotide sequence or synthetic tail into the $\alpha 3$ or mu domain of the heavy chain or any $\alpha 3$ or mu domain-modified heavy chain expressed by the host and having retained specific binding affinity in the absence of a light chain.

A) Applicants' allegations on p. 17 of the Response of 10/31/07 and the Declaration of Dr. Vitale have been considered but are not found persuasive.

Applicants' allege that the specification and the one skilled in the art having a general knowledge such as an undergraduate biology student could practice the invention without undue experimentation.

The examiner submits that because the combination of potential modifications that could be made to the amino acid residues anywhere within the 18 C-terminal

residues of a heavy chain comprising an alpha-3 or mu domain is innumerable, and because some residues can be substituted with "*any amino acid*" or the nucleotide encoding the amino acid sequence could comprise one or any combination of

- a) one or more point mutations
- b) one or more nucleic acid deletions
- c) one or more nucleic acid additions, *and*
- d) one or more nucleotides replaced with a synthetic nucleotide sequence,

that it would require undue experimentation for one of ordinary skill in the art to practice the invention. More guidance is required for one of ordinary skill in the art to reproduce the invention and render the reproducibility without undue burden.

Further, Applicants have not addressed the predictability factor in Wands which requires that one of skill in the art could predict based on the specification that a reasonable number of antibodies could be produced from any combination of modifications as presently recited in the claims. As discussed above, the specification is not enabling for making the full breath of embodiments where just "*any amino acid*" can be substituted into the C-terminus or the nucleotide encoding the amino acid sequence could comprise one or any combination of

- a) one or more point mutations
- b) one or more nucleic acid deletions
- c) one or more nucleic acid additions, *and*
- d) one or more nucleotides replaced with a synthetic nucleotide sequence.

An “undergraduate in biology” could not reasonably expect or predict that the heavy chain produced by the method would have reduced vacuolarization, proper folding with a light chain *and* antigen binding. For example, refer to the references of record describing the unpredictability of amino acid substitutions in protein chemistry in general (Ibragimova and Wade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198); Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138); Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252); Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987); and Lin et al Biochemistry USA Vol 14:1559-1563 (1975)). It is well known in the art that when modifying an amino acid of a protein, one can expect the 3-dimensional denaturation of the protein.

The specification demonstrates that the NVSVSV sequence is responsible for the vacuolar targeting of the antibodies produced by plants, and more particularly by *Nicotiana tabacum*. Based on the specification, it is not clear whether the NVSVSV sequence has any chance of being recognized by plants other than *Nicotiana tabacum*. The method of Claim 1 encompasses expressing the antibody in any host cell, but it is not clear from the specification that vacuolar sorting signals would be the same between, for example, mammalian cells, yeast or plants. Absent a showing to the contrary (further experiments or supported reasoning), the specification is only enabling for the modified NVSVSV sequence for use in expressing antibodies, where the host cell is *Nicotiana tabacum*.

B) Applicants have not addressed the section of the Office Action where the examiner rejected the claims on the basis of producing only a single heavy chain

antibody. In the Office Action, the examiner asserted that one of skill in the art recognized at the time of Applicant's filing date, that both heavy and light chains, or at least the full complement of CDRs from both a heavy and light chain, were required to be present in an antibody molecule in order for the antibody molecule to bind to the antigen of interest. The rejection was based in the breadth of the claims for producing only a heavy chain in the absence of a corresponding light chain or in the absence of the light chain CDRs. Thus the scope of Applicants claimed method encompasses producing a single heavy chain which allegedly is reduced in vacuolarization and retains antigen binding. Applicants should understand that implicit in producing the antibody molecule with reduced vacuolarization, is the requirement that the antibody molecule have a use under 112, 1st paragraph. It is the examiner's position that the heavy chain produced by the claimed method could not be used and therefore would not have a practical use, i.e., antigen binding, much less that it is unpredictable that the heavy chain alone would bind antigen, thus it is not clear how the claim scope encompassing producing modified single heavy chains would meet the requirements under 112, 1st paragraph.

Applicants' response is incomplete, and therefore the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

29. The rejection of Claims 1, 34, 35, 38, 40, 41, 46, 48 and 50 under 35 U.S.C. 103(a) as being unpatentable over Frigerio et al. (Plant Physiology 123:1483-1493 (August 2000); cited in the IDS of May 18, 2005 and the PTO 892 form of 2/2/07) in view of Vitale and Raikhel (Trends in Plant Science 4(4):149-155 (April 1999); cited in the IDS of May 18, 2005 and the PTO 892 form of 2/2/07), Koide et al. (Plant Cell Physiol. 40(11):1152-1159 (1999); cited in the IDS of and the PTO 892 form of 2/2/07) and Matsuoka et al. (J. Exp. Bot. 50:165-174 (1999); cited in the IDS of 5/18/05) is maintained.

Applicants' allegations on pp. 18-19 of the Response of 10/31/07 and the Declarations of Drs. Vitale and Frigerio have been carefully considered but are not found persuasive.

The allegations that are presented are essentially that the named inventors at the time of the instant method invention were the first to realize *and* identify human proteins containing cryptic sorting signals that could be used to target human proteins to a particular location in plants.

The examiner respectfully disagrees with Applicants allegation that no knowledge or awareness of signaling sequences in human proteins existed in the prior art before or at the time of their invention. The knowledge of signaling sequences more especially in view of the Frigerio reference which fully contemplated the existence of cryptic sequence residues that mediated heterologous proteins in vacuole trafficking with the extrapolation of this possibility to the hybrid IgA/G antibodies used in their study belies Applicants assertion. The declarants have not addressed how or why *with* this information in the Frigerio reference, one skilled in the art would not have been motivated to have produced by plant expression methods an antibody that would not be sequestered in vacuoles but instead secreted in abundance by modifying the signal sequences. Thus the rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

30. Claims 39, 43, 44 and 87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 39 and 44 are indefinite for failing to include a period at the end of the claim, thus one of skill in the art could not determine the metes and bounds because it is unclear if additional subject matter is intended.

b) Claim 43 is indefinite for the recitation in element (iii) "an isoleucine to amino acids from the C-terminus" because it is not clear where the isoleucine should be positioned with reference to the C-terminus.

c) Claim 87 is indefinite for reciting improper Markush group language. See MPEP 803.02.

Conclusion

31. No claims are allowed.

32. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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